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(54) Title: COMPOSITION OF CISPLATIN IN COMBINATION WITH 2,2'-DITHIO-BIS(ETHANESULFONATE) (DIMESNA) (57) Abstract <p>Co-administration of cisplatin with a pharmaceutically acceptable form of 2,2'-dithio-bis(ethanesulfonate) reduces the nephrotoxicity and myelosuppression of cisplatin and potentiates its anti-tumor action. Preferably the cisplatin and sulfonate are formulated as a composition, especially a sterile injectable solution containing chloride ions and sodium and hydrogen cations.</p>			

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COMPOSITION OF CISPLATIN IN COMBINATION WITH 2,2'-DITHIO-BIS(ETHANESULFONATE)
(DIMESNA)

BACKGROUND OF THE INVENTION

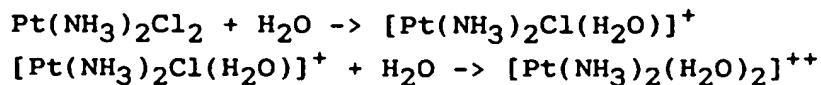
1. FIELD OF THE INVENTION

This invention concerns a composition of cis-
5 diammine dichloroplatinum (cisplatin), the widely used
anti-cancer drug.

2. DESCRIPTION OF THE RELATED ART

One of the most important and common dose-limiting
toxicities of cisplatin is nephrotoxicity (causing
10 renal damage). In order for cisplatin to react with
certain nucleic acid sequences in cellular DNA, it must
first undergo chemical conversion to an active species
by the displacement of chloride ligands with water to
form the mono-aquo or di-aquo species. The aquo species
15 of cisplatin is reactive with nucleophilic species,
including the imidazole nitrogens on DNA or sulfhydryl
groups which are also present in cells forming the renal
tubular epithelium in humans.

Cisplatin readily reacts with compounds containing
20 sulfhydryl moieties. Sulfhydryl groups are found in
cysteine, glutathione and homocysteine. Metallothionein
is a 7 kDa protein containing about 30% cysteine residue.
Increased cellular concentrations of metallothionein
25 and glutathione have been correlated with drug
resistance to cisplatin therapy. Thus, if the local
renal tubular concentration of sulfhydryl groups from 2-
mercaptoethanesulfonate could be increased, then cisplatin
30 toxicity might be reduced by the chemical quenching
in the renal tubules of the reactive cisplatin "aqua
species". The aquo species are formed by hydrolysis of
cisplatin according to the following equations:



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Kempf et al., British J. Cancer, 52, 937-939 (1985) describe the use of sodium 2-mercaptopethanesulfonate ("mesna") to prevent the nephrotoxicity of cisplatin in the kidneys of rats. This paper states that the only 5 known metabolite of mesna is its disulfide, dimesna, which is incapable of reaction with cisplatin. According to this paper, after i.v. administration of mesna, the disulfide is formed spontaneously by autoxidation and found predominantly in the bloodstream. The disulfide is then eliminated by the kidneys. These authors gave cisplatin i.v. to rats and also gave mesna orally 2 hours before each cisplatin injection and then several times daily for 4 days after the last cisplatin injection.

15 The treatment regime proposed by Kempf et al. is complex and impractical. However, mesna cannot be co-administered with cisplatin, since it would react with it. It has been a problem to find an alternative to mesna which can be co-administered with cisplatin.

20 SUMMARY OF THE INVENTION

It has now surprisingly been found that 2,2'-di-thio-bis(ethanesulfonate), especially in the form of its sodium salt, dimesna, can be administered substantially simultaneously or near-simultaneously with cisplatin. 25 The sulfonate is not attacked by cysteine and other thiol proteins in the bloodstream and yet is effective to reduce the nephrotoxicity of cisplatin. This is particularly surprising because there is a suspicion that mesna reacts with cysteine in the bloodstream. 30 Increased cysteine elimination in the urine has been reported in association with the administration of mesna to human subjects: see B. Sidau and I.C. Shaw, J. Chromatography 311, 234-238, (1984). If the metabolism of mesna to dimesna, as stated in the above-mentioned Kempf 35 et al. paper is significant, then possibly the dimesna

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is reacting with cysteine. Alternatively, if mesna is reacting with cysteine, perhaps dimesna is not a significant metabolite of mesna.

Mesna is widely used to reduce or prevent the risk
5 of hemorrhagic cystitis to the uroepithelium, which causes bleeding in the ureters, bladder and urethra, a condition which is associated with the use of certain oxazaphosphorine anticancer drugs which include cyclophosphamide, ifosfamide and trophosphamide. Dimesna has
10 been tested for the same purpose: see Brock et al., J. Cancer Res. Clin. Oncol. 108, 87-97 1984 and Eur. J. Cancer Clin. Oncol. 17, 1155-1163 (1981). Oxazaphosphorine-induced uroepithelial toxicity is chemically, biochemically, anatomically and pathologically distinct
15 from the renal toxicity which is observed with administration of cisplatin. In the case of oxazaphosphorines, acrolein is produced as a toxic metabolite and mesna undergoes addition to the double bond of acrolein, resulting in a stable thioether adduct which has no
20 damaging effects on the uroepithelium and is excreted in the urine.

According to one aspect of the present invention, there is provided a composition suitable for administration to human patients with cancer, comprising cisplatin
25 and a pharmaceutically acceptable form of 2,2'-dithio-bis(ethanesulfonate). The sulfonate may be in the form of any pharmaceutically acceptable salt, especially the disodium salt (dimesna) or as the free acid or a mixture thereof. Preferably it is in the form of the
30 sodium salt. The preferred form of composition is an aqueous solution, which will normally be a sterile injectable aqueous solution. Such a solution will therefore contain 2,2'-dithio-bis(ethanesulfonate) anions and pharmaceutically acceptable cations, especially Na^+ and H^+ , to provide electrical neutrality.
35

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Use of a composition of the invention will help to ensure that the patient receives the correct dose, will reduce errors in prescribing two drugs and will reduce the amount of additional prophylactic measures needed to 5 reduce nephrotoxicity and avoid iatrogenic related complications (furosemide or hypertonic saline administration - see below).

Compositions of the invention have also been found to potentiate antitumor activity in animal tests. They 10 can also protect against cisplatin-induced myelosuppression or neurotoxicity.

The invention further provides the use of a pharmaceutically acceptable form of 2,2'-dithio-bis(ethanesulfonate), especially the disodium salt (dimesna), in the 15 manufacture of a medicament for administration in combination with cisplatin to a human patient at substantially the same time or sequentially, in either order, especially within 24 hours of one another, whereby the sulfonate and cisplatin become co-present in the blood 20 of the patient. Where patent law permits, notably in Australia, this concept may be expressed alternatively in terms of a method of administering the sulfonate and the cisplatin to the patient at substantially the same time, as set forth above. Thus, this invention further 25 enables the sulfonate and cisplatin to be given sequentially, in either order, especially within 24 hours of one another, or near enough together in time so that the sulfonate enters the bloodstream when the cisplatin is present therein or the cisplatin enters the bloodstream 30 when the sulfonate is present therein, so that the principle of the invention (reduction of nephrotoxicity of cisplatin by the concurrent action therewith *in vivo* of 2,2'-dithio-bis(ethanesulfonate) can have effect.

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Brief Description Of The Drawings

Figures 1 to 3 Values on day 5 post treatment
with i.v. cisplatin (6 mg/kg) with or without increasing
doses of i.v. 2,2'-dithio-bis(ethanesulfonate)
5 (BNP7787):

- Fig. 1: serum creatinine (mg/dl); Fig. 2: BUN (Blood urea nitrogen)(mg/dl); Fig. 3: WBC (White blood counts)(thousands of counts/mm³)

Figures 4 and 5 Responses of colon tumor-bearing
10 Fischer rats injected i.v. with cisplatin and 2,2'-dithio-bis(ethanesulfonate) (BNP7787):

- Fig. 4: median tumor weight (mg.) vs. days
- Fig. 5: mean body weight (% starting weight) vs. days

DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 The composition of the invention will typically be a solution. It can take any form appropriate to or conventional for formulation of cisplatin, which is not incompatible with the co-presence of the sulfonate or the action of cisplatin. The type of formulation will
20 of course depend on the route of administration, which will normally be parenteral and preferably by injection.

Hereinafter, the invention will be discussed mainly with reference to sterile aqueous solutions of disodium 2,2'-dithio-bis(ethanesulfonate) (dimesna), but the
25 person skilled in the art will readily be able to use the principles of this invention in relation to other formulations of cisplatin and other forms of the sulfonate. Said other forms include the monosodium, monopotassium., sodium-potassium, dipotassium, calcium and
30 magnesium salts of the sulfonate.

Normally the aqueous solution will have a pH less than 7.0 and greater than 1.0, most usually between 2 and 6 and preferably between 4 and 6. This will help to prevent formation of an aquo species of cisplatin.
35 The same pH also serves to prevent the formation of

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mesna, which could then react with cisplatin species. Preferably hydrochloric acid or phosphoric acid is used to reduce the pH. The solution will preferably contain chloride ion, e.g. provided as NaCl and optionally 5 augmented by use of HCl to reduce the pH, because the stability of cisplatin is proportionally related to the chloride ion concentration of the solution. Also, a high concentration of chloride in the plasma provides conditions which largely favor the maintenance of the 10 unreactive neutral dichloro species of cisplatin. The neutral dichloro cisplatin species can enter cells, such as cancer cells, and because the chloride concentration inside of the cell is low, the conversion of cisplatin dichloro species to mono-aquo or di-aquo 15 species is favored. The aquo cisplatin species is then available to form coordinate chelate crosslinks with certain nucleic acids in cellular DNA.

Cisplatin-induced nephrotoxicity is a clinically important problem and is associated with a decrease in 20 creatinine clearance, elevated creatinine, elevated blood urea nitrogen, elevated uric acid and hypomagnesemia. Prophylactic measures generally used to try to reduce the risk of this complication include:

- a. Parenteral administration of hypertonic (3%)
25 NaCl;
- b. Mannitol diuresis;
- c. Pre- and/or post-treatment hydration (oral or parenteral);
- d. Forced diuresis by the administration of loop
30 diuretics such as furosemide; or
- e. Oral or parenteral administration of thiosulfate.

These measures introduce additional risks for patients undergoing treatment. For example, the administration 35 of hypertonic saline (NaCl 30 mg/ml) poses the

risk of iatrogenic hypernatremia. Hypernatremia is a life-threatening medical emergency and the administration of hypertonic saline is contra-indicated in patients with elevated serum sodium or patients with
5 congestive heart failure. The use of powerful loop diuretics to increase urine production by the kidney, such as furosemide, increases the iatrogenic risk of hypokalemia, hyponatremia, hypocalcemia, hypovolemia, metabolic alkalosis and hypochloremia. All of these
10 conditions can be life-threatening. They are avoidable by the practice of this invention.

One preferred embodiment of this invention is an injectable, sterile, stable aqueous solution or suspension, which comprises cisplatin, 2,2'-dithio-bis(ethanesulfonate), sodium chloride and hydrochloric or phosphoric acid, especially in a unit dosage form. To preserve sterility, it is stored in a sealed container. This solution is particularly suitable for intravenous injection in human patients with cancer. Preferably
20 the concentration of cisplatin is between about 0.1 mg/ml and about 1.0 mg/ml. Preferably the concentration of 2,2'-dithio-bis(ethanesulfonate) is between 1 mg/ml and its maximum solubility, which, for dimesna, is about 320 mg/ml (measured in either water or saline
25 solution), more preferably between 5 mg/ml and 100 mg/ml (reckoned as the disodium salt). Preferably the concentration of sodium chloride is between 1 and 25 mg/ml, more preferably between 9 and 25 mg/ml and the hydrochloric or phosphoric acid is in a concentration sufficient to provide or maintain the pH in the range of 2 to
30 6, more preferably 4 to 6. Desirably, the composition also contains a buffer to maintain the pH, especially sodium acetate or phosphate, alone or in combination.

Preferably, the composition of the invention contains mannitol, e.g. where the composition is a solu-

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tion, usually in a concentration between about 10 and about 25, more preferably between 10 and 15 mg/ml.

The composition of the invention can be prepared by mixing the ingredients in any order.

5 The same relative proportions of the active principles and of the optional other ingredients can be used to prepare other compositions of the invention. Thus the weight ratio of cisplatin to the sulfonate (reckoned as disodium salt) is preferably from 1:1 to 1:3200 and
10 more preferably from 1:5 to 1: 1000.

When other salts of 2,2'-dithio-bis(ethanesulfonate) are used in place of the disodium salt, the concentration or proportion of the sulfonate will be adjusted according to molarity. 1 g of the disodium salt,
15 dimesna, is equivalent to 4.63 millimoles of 2,2'-di-
thio-bis(ethanesulfonate) anion.

20 The 2,2'-dithio-bis(ethanesulfonate) is preferably prepared in lyophilised form, whether for subsequent admixture with cisplatin or for separate administration before or after cisplatin. Aqueous solutions or lyophili-
lates of the sulfonate are stable over a wide pH range, especially 1.5 to 9. Thus, when the sulfonate is administered separately, a pH range of 4 to 9 is preferred.
25 The cisplatin-sulfonate compositions of the invention are also preferably stored as lyophiliates. Lyophiliates can be reconstituted with sterile water, dextrose (5%) and water, "normal" physiological saline or lactated Ringer's solution. The reconstituted solution is then preferably filtered through a sterile 0.2 micrometre
30 filter, to avoid microaggregation of the drug product.

35 Administration of cisplatin or a composition of the invention containing it will normally be parenteral, e.g. intravenous, intraarterial, intraperitoneal, subcu-
taneous, intracavitory or intrapleural. The preferred mode is by injection of an aqueous solution or suspen-

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sion, preferably intravenously. The sulfonate can be administered separately from the cisplatin parenterally (as above) or orally.

Various regimes of combination administration are
5 possible, e.g. (a) as a one time administration of a composition of the invention, (b) first administering the sulfonate and then the cisplatin within 24 hours or (c) first administering the sulfonate, then the cisplatin one hour later, followed by simultaneous administration
10 of the cisplatin and the sulfonate and, one hour after completion of the cisplatin administration, further sulfonate.

Where the sulfonate is given orally, it can be formulated in any form conventional in the art of pharmaceutical formulation. Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. They may contain an excipient, e.g. sodium citrate or dicalcium phosphate, or a carrier. Other optional additives may comprise a filler, binder, humectant, disintegrating agent, solution retarder, absorption accelerator, wetting agent, adsorbent, lubricant or buffering agent, as well known in the pharmaceutical formulation art.
15
20

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using excipients such as lactose or milk sugar as well as high molecular weight polyethylene glycols, and the like.
25

Preferably the composition is formulated for the delayed release of the 2,2'-dithio-bis(ethanesulfonate) in a certain part of the intestinal tract. Examples of embedding agents for such compositions are polymeric substances and waxes.
30

Liquid dosage forms for oral administration include physiologically acceptable emulsions, solutions, suspen-
35

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sions, syrups, and elixirs.

The composition of the invention can be given to a patient who has not been treated with an anti-cancer agent (untreated) or to a patient who has previously 5 been treated or exposed to anti-cancer agent(s). Also, it can be administered to patients with cancer in combination with another anti-cancer agent or agents, especially 10 5-FU, bleomycin, VP-16 (etoposide), cyclophosphamide, ifosfamide, leucovorin, methotrexate, or vinblastine.

The following non-limiting Examples illustrate the invention. The vials referred to are "amber vials", which protect the cisplatin from exposure to fluorescent light.

15

EXAMPLE 1

(a) Preparation of 2,2'-dithio-bis(ethanesulfonate)

Disodium 2,2'-dithio-bis-(ethanesulfonate) was prepared by oxidizing 2-mercaptoethanesulfonate in water 20 with an equimolar amount of iodine as previously reported by L. Lamaire and M. Reiger, J. Org. Chem. 26, 1330-1, (1961).

(b) Stability of 2,2'-Dithio-Bis-Ethane Sulfonate

50 mg. of the sulfonate thus prepared were dissolved in 1 ml. of water and the pH of the solution 25 adjusted to 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 by adding 1N hydrochloric acid in water or the pH adjusted to 8.0, 9.0, 10.0 or 11.0 by adding 1 N sodium hydroxide in water. The solution was then stirred for 24 hours at 30 room temperature, the water was removed at reduced pressure and the residue dissolved in spectral grade D₂O. The proton NMR spectrum gave only peaks corresponding to the starting material.

Heating the pH 1.5 solution to 100 deg. C for 10 35 minutes gave no change in the proton NMR spectrum.

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Note that mesna and dimesna show distinctive peaks, whereby degradation of dimesna to mesna could be monitored. The proton NMR spectrum of mesna provided multiplets at 2.886 and 3.196, dimesna at 3.096.

5 (c) Preparation of a stable solution of cisplatin and 2,2'-dithio-bis(ethanesulfonate)

Pure hydrochloric acid (99.999%) was added to a sterile, injectable, aqueous 0.9% w/v solution of sodium chloride (US Pharmacopeia grade), to give a pH in
10 the range 2.0 to 6.0. 1 mg./ml. of the above NaCl solution of pure cisplatin was added and allowed to completely dissolve by agitation (1500-2500 rpm) at room temperature, for approximately 60 to 90 minutes in the dark. Then, 15 mg of dimesna, prepared above, per ml.
15 of solution were added and the mixture agitated until complete dissolution occurred. The final pH was adjusted to within the range pH 2.0 to 6.0 by adding further pure hydrochloric acid. The solution was sterilized by filtration through a sterile 0.2 micrometre filter
20 (obtained from VWR Scientific) and stored in sterile injection vials. Each vial contained approximately 0.9 mg of cisplatin and 14.3 mg of 2,2'-dithio-bis(ethane-sulfonate) per ml of solution.

25

EXAMPLE 2

To a sterile injectable aqueous solution of 0.9% w/v sodium chloride (USP grade) were added 15 mg/ml of NaCl solution of dimesna, which was allowed to dissolve completely by agitation (1500-2500 rpm) at room temperature, for 5-10 minutes. The pH of the solution was adjusted to within the range 2.0 to 6.0 by adding pure (99.999%) hydrochloric acid. 1 mg/ml of dimesna solution of pure (99.999%) cisplatin was added and the mixture agitated in the dark until complete dissolution
30
35 occurred. The remaining steps were as in Example 1(c),

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giving a solution of the same approximate composition.

EXAMPLE 3

Example 2 was repeated except that to a 15 mg/ml
5 sterile aqueous solution of dimesna were added 9 mg/ml
of dimesna solution of NaCl crystals. Each vial con-
tained approximately 1.0 mg of cisplatin and 14.3 mg of
dimesna per ml. of injection solution.

10

EXAMPLE 4

Example 1(c) was repeated except that 0.5 mg./ml.
of cisplatin and 30 mg./ml. of dimesna were used. Each
vial contained 0.5 mg of cisplatin and 30.0 mg of dimes-
na per ml of injection solution.

15

EXAMPLE 5

Example 1(c) was repeated except that USP grade
potassium chloride crystals were dissolved in the acidic
NaCl solution to give a concentration of 0.1% w/v KCl
20 and also that 30 mg/ml dimesna were used. Each vial
contained 1.0 mg of cisplatin and 30.0 mg of dimesna per
ml of injection solution.

EXAMPLE 6

25 Example 1(c) was repeated except that pure mannitol
(99+% purity, purchased from Aldrich Chemical Company)
was dissolved in the NaCl solution, to give a concentra-
tion of 1.0% w/v mannitol, and also that 30 mg/ml of
dimesna were used. Each vial contained approximately
30 1.0 mg of cisplatin and 30.0 mg of dimesna per ml of
injection solution.

EXAMPLE 7

Example 1(c) was repeated except that the unfiltered,
35 acidified NaCl solution containing cisplatin and 2,2'-

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dithio-bis(ethanesulfonate) was lyophilized using commercially available equipment. The lyophilate can be stored at room temperature in amber vials, which are shielded from light for 6 months to one year until 5 needed for administration to a patient. It can be reconstituted with sterile water (USP), if necessary re-acidified to a pH of 2.0 to 6.0 with hydrochloric or phosphoric acid, and the solution passed through a sterile 0.2 micrometre filter.

10

EXAMPLE 8

In Vivo Demonstration of Protection by 2,2'-Dithio-Bis-(Ethanesulfonate) (BNP7787) Against Cisplatin-induced Nephrotoxicity and Myelosuppression in Fischer Rats.

15 This Example shows the in vivo protective effects of 2,2'-dithio-bis(ethanesulfonate) (= BNP7787) administered at 1,000 mg/kg by a single i.v. injection in Fischer rats (150 - 200g) receiving a nephrotoxic dose of cisplatin (6 mg/kg i.v. single injection) when the 20 two drugs are administered concurrently (substantially contemporaneously).

Under Good Laboratory Practice conditions, Fischer rats (10 per treatment group) were treated as follows:

- Group 1: no treatment
25 Group 2: normal physiological saline
Group 3: 1000 mg/kg of BNP7787
Group 4: 6 mg/kg cisplatin
Group 5: 6 mg/kg cisplatin and 37 mg/kg BNP7787
Group 6: 6 mg/kg cisplatin and 111 mg/kg BNP 7787
30 Group 7: 6 mg/kg cisplatin and 333 mg/kg BNP 7787
Group 8: 6 mg/kg cisplatin and 1000 mg/kg BNP 7787

Creatinine (Figure 1), serum blood urea nitrogen (BUN) (Figure 2), each in mg/dl and mean plasma white blood cell counts, in thousands/mm³ (Figure 3) were 35 measured on day 5 and the animals were weighed daily.

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Figures 1 to 3 display the results in the form of bar charts in which Groups 1 to 8 are arranged in order from left to right. As shown in Figures 1 and 2, BNP7787 demonstrates significant renal protection (100% at 333 5 and 1000 mg/kg of BNP7787). As shown in Figure 3, the higher (333 and 1000 mg/kg) doses of 2,2'-dithio-bis-(ethanesulfonate) gave WBCs of approximately 6,800 and 6,200, respectively. These are within 15% of the WBC values for untreated controls. The day 5 mean WBC counts 10 for the cisplatin-only and low dose (37 mg/kg) 2,2'-dithio-bis-(ethanesulfonate) treatment groups are approximately 4,800 and 4,500, respectively and represent a 32% to 36% reduction from the untreated control group. The Fischer rat model is highly correlated with cisplatin-induced nephrotoxicity in humans.

Thus, this study evidences a dose-dependent effect of 2,2'-dithio-bis(ethanesulfonate) in providing renal protection from cisplatin-induced nephrotoxicity and myelosuppression, including 100% renal protection at 20 higher doses of the sulfonate.

EXAMPLE 9

Potentiation of Cisplatin Antitumor Activity by Parenteral Administration of 2,2'-dithio-bis(ethane sulfonate)

25 The antitumor activity and toxicity, as measured by weight changes estimated by changes in tumor volumes and animal weights, respectively, of escalating doses of intravenously administered cisplatin (6 mg/kg and 9 mg/kg) with or without substantially contemporaneously 30 intravenously administered BNP7787 (1000 mg/kg) was investigated in Fischer rats bearing subcutaneously established (approx. 3.0 g) WARD colon cancer tumors. The WARD tumors will grow in the untreated control rats from 3.0 g to about 10 g in about 7 days.

35 The results are shown plotted in Figures 4 and 5, where

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- mean body weight (Fig. 4) and median tumor weight (Fig. 5) are plotted on the ordinate against time in days on the abscissa. In both Figures, the key is as follows:
- Open circle = untreated, control
- 5 Filled circle = BNP 7787, 1000mg/kg
- Open inverted triangle = cisplatin (CDDP), 6 mg/kg
- Filled inverted triangle = cisplatin, 9 mg/kg
- Open square = cisplatin, 6 mg/kg, plus BNP7787, 1000mg/kg
- 10 Filled square = cisplatin, 9 mg/kg, plus BNP7787, 1000mg/kg

As seen in Figure 4, untreated tumor-bearing rats treated with BNP7787 lose only about 2 to 4 % of their body weight in about 6 days, whereas rats treated with 15 cisplatin alone (6 mg/kg and 9 mg/kg) lose up to 8 % of their body weight at 6 days. Treatments with i.v. BNP7787 (1000 mg/kg) at both dose levels of cisplatin (6 mg/kg and 9 mg/kg) were clearly protective against renal damage, as the rats put on more weight than those in all 20 other treatment groups (compare open and closed squares to open and closed triangles). This observation suggests that treatment with BNP7787 may prevent or reduce other cisplatin-associated toxicities, including neuro-toxicity and emesis, leading to weight loss in rats.

25 Moreover, BNP7787 potentiated cisplatin antitumor activity for both the 6 mg/kg and 9 mg/kg dose groups (Figure 5-open and closed squares, respectively). Rats treated with cisplatin only at doses of 6 mg/kg and 9 mg/kg had a maximum reduction in median tumor weight 30 from 3,000 mg to 700 and 500 mg, respectively. Rats treated with cisplatin at doses of 6 mg/kg and 9 mg/kg immediately followed by BNP7787 using a single i.v. dose of 1,000 mg/kg had a maximum reduction in median tumor weight from 3,000 mg to less than 300 and 100 mg, respectively.

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CLAIMS

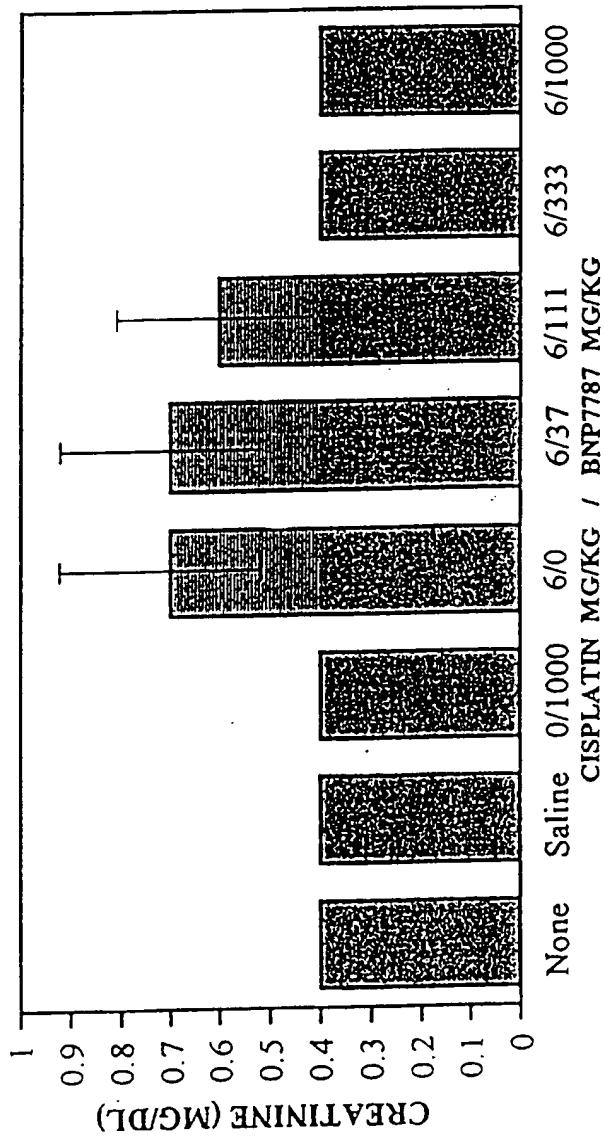
1. A composition suitable for administration to human patients with cancer, comprising cisplatin and a pharmaceutically acceptable form of 2,2'-dithio-bis(ethanesulfonate).
2. A composition according to claim 1 in the form of a sterile injectable aqueous solution or suspension of pH 2 to 6.
3. A composition according to claim 2 wherein the pH is from 4 to 6.
4. A composition according to claim 2 or 3, further comprising a buffer.
5. A composition according to claim 2, 3 or 4, which contains chloride anions and sodium and hydrogen cations.
6. A composition according to claim 5, which comprises 0.1 to 1.0 mg/ml of cisplatin, 1.0 to 320 mg/ml of the sulfonate, 10 to 25 mg/ml of sodium chloride and hydrochloric or phosphoric acid to provide the defined pH.
7. A composition according to claim 6, which further comprises from 10 to 25 mg/ml of mannitol.
8. A composition according to claim 1, 2, 3, 4, 5, 6 or 7, in the form of a lyophilate.
9. Use of a pharmaceutically acceptable form of 2,2'-dithio-bis(ethanesulfonate) in the manufacture of a medicament for administration in combination with cisplatin to a human patient, at substantially the same time or sequentially, whereby the sulfonate and cisplatin become co-present in the blood of the patient.
10. Use according to claim 9 of a lyophilized form of an aqueous solution of the sulfonate.

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Figure 1. Serum Creatinine Values on Day 5 Post Treatment with i.v. Cisplatin (6 mg/kg) With or Without Increasing Doses of i.v. 2,2'-Dithio-Bis-Ethane Sulfonate (BNP7787).

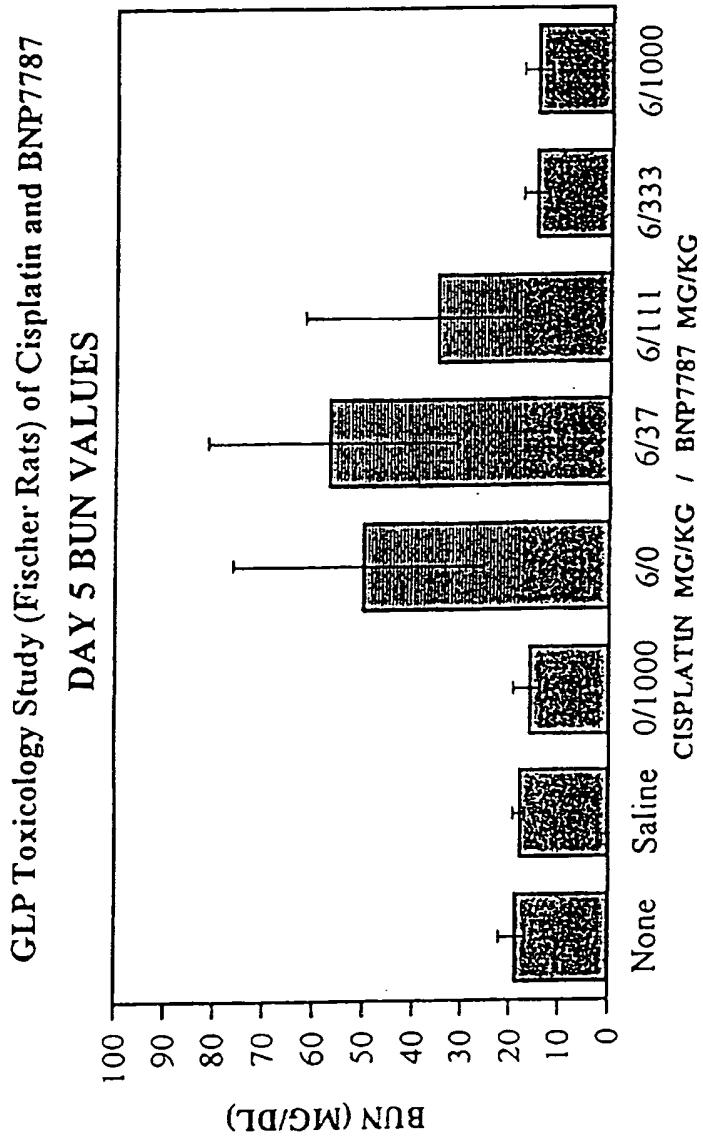
GLP Toxicology Study (Fischer Rats) of Cisplatin and BNP7787

DAY 5 CREATININE VALUES



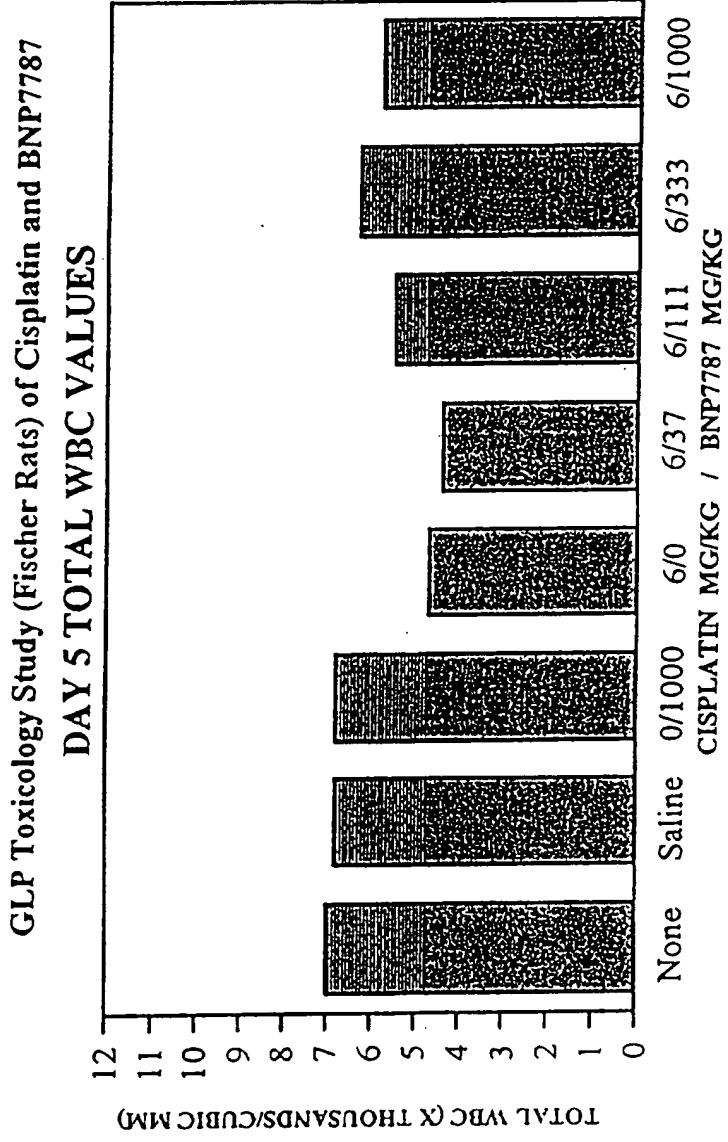
2 / 5

Figure 2. Serum BUN (Blood Urea Nitrogen) Values on Day 5 Post Treatment with i.v. Cisplatin (6 mg/kg) With or Without Increasing Doses of i.v. 2,2'-Dithio-Bis-Ethane Sulfonate (BNP7787).



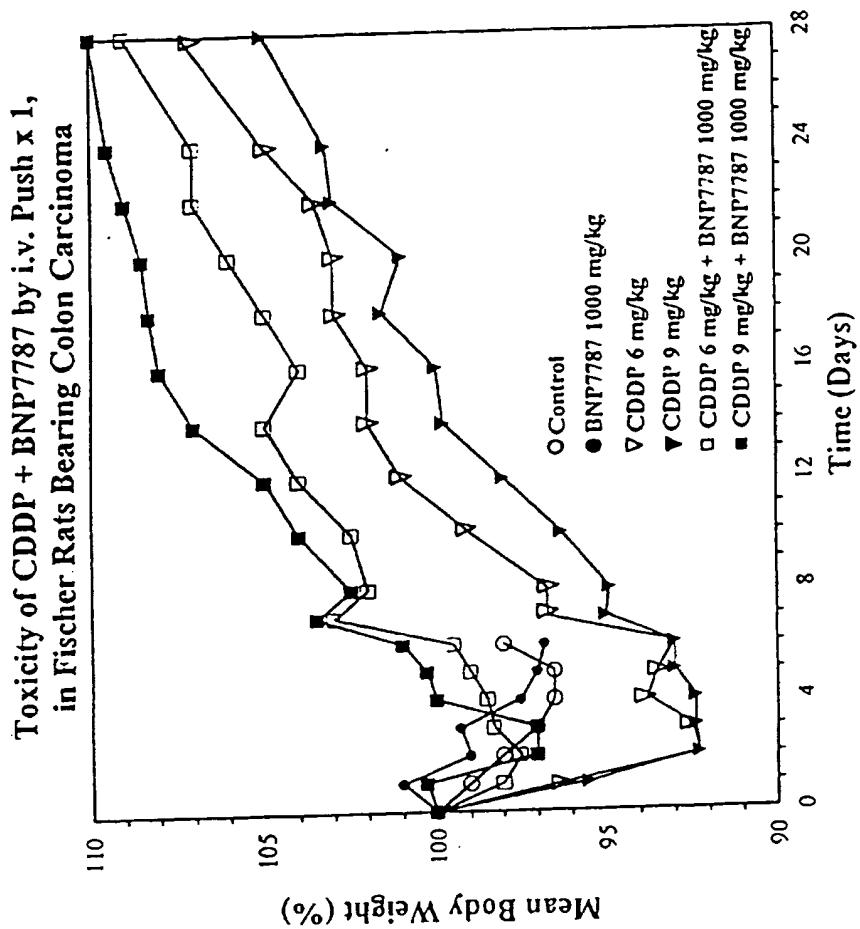
3 / 5

Figure 3. Total WBC Values on Day 5 Post Treatment with i.v. Cisplatin (6 mg/kg) With or Without Increasing Doses of i.v. 2,2'-Dithio-Bis-Ethane Sulfonate (BNP7787).



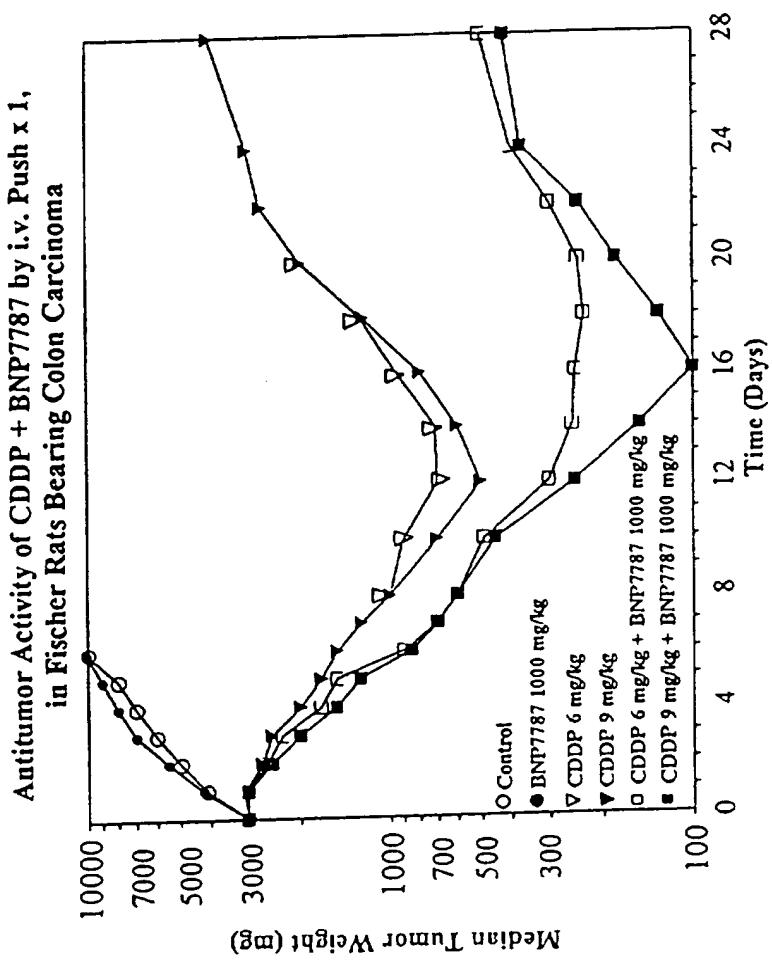
4 / 5

Figure 4. Weight Change in Tumor Bearing Fischer Rats Treated with Parenteral Cisplatin (6 mg/kg or 9 mg/kg) and 2,2'-Dithio-Bis-Ethane Sulfonate (BNP7787 @ 1,000 mg/kg)



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Figure 5. Antitumor Response of Tumor Bearing Fischer Rats Treated with Parenteral Cisplatin (6 mg/kg or 9 mg/kg) and 2,2'-Dithio-Bis-Ethane Sulfonate (BNP7787 @ 1000 mg/kg).



INTERNATIONAL SEARCH REPORT

Internal Application No	PCT/EP 95/04490
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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K33/24 A61K31/185 // (A61K33/24, A61K31:185)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUR J CANCER, vol. 27, no. 10, 1991 pages 1243-1247, O.R. LEEUWENKAMP ET AL. 'Reaction kinetics of cisplatin and its monoaquated species with the modulating agents (di)mesna and thiosulphate' see abstract see the whole document -----/-	1,9
Y		1-10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- *'E' earlier document but published on or after the international filing date
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Date of the actual completion of the international search

1 April 1996

Date of mailing of the international search report

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Stierman, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/04490

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	D. SCHMÄHL 'Combination effects in chemical carcinogenesis' 1988 , ED. WEINHEIM, VCH PUBLISHERS see page 153 - page 173 see page 162 - page 166 ---	1-10
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Y	EUR J CANCER CLIN ONCOL, vol. 17, 1981 pages 1155-1163, N. BROCK ET AL. 'Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention.' cited in the application see the whole document see page 1158 ---	1-10
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Y	EP,A,0 538 858 (SQUIBB BRISTOL MYERS CO) 28 April 1993 see the whole document ---	1-10
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International Application No

PCT/EP 95/04490

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